REMARKS

The Official Action dated April 26, 2011 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present amendment, claim 12 is amended to clarify that the polarizing filter is for collecting backscattered light which has been subjected to multiple scattering events in the tissue and to more clearly define the computing device. Withdrawn claims 1 and 23 are similarly amended to clarify that the backscattered light has been subjected to multiple scattering events in the tissue and for matters of form. Support for these amendments may be found in the present application, for example, at pages 8-9. It is believed that these changes do not involve any introduction of new matter, whereby entry of the amendments is in order and is respectfully requested.

According to claim 12, the system for determining microcirculation of a living tissue according to the present invention comprises (i) a white light source and a filter capable of illuminating a tissue surface with polarized light, (ii) a polarizing filter adapted to collect backscattered light subjected to multiple scattering events in the tissue; (iii) a photosensitive array capable of detecting the backscattered and polarized light and converting the detected light to a collected information of digital values; and (iv) a computing device adapted to receive said collected information, adapted to separate the collected information into data matrixes representing red, blue and green colors, respectively, and adapted to employ an algorithm using the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation.

Thus, the presently claimed system determines microcirculation based on the concentration of red blood cells. As explained in the specification, for example at pages 8-9, "red" photons have a tendency to be less absorbed by the red blood cells than "green" and "blue" photons, and, consequently, the more red blood cells in the tissue, indicative of a higher degree of vasodilatation, the higher is the absorption of "green" and "blue" photons in relation to the absorption of "red" photons in the polarized white light which reaches the tissue surface.

The backscattered light has been subjected to multiple scattering events in the tissue. In conventional devices, such multiple scattering undesirably causes distortion in an image produced from the backscattered light. However, such distortion from multiple scattering can be significantly reduced in the presently claimed system as the computing device is adapted to separate the collected information into data matrixes representing red, blue and green colors, respectively, and is adapted to employ an algorithm using the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation. Importantly, the digital values are separated into the red, blue and green data matrixes which are then used to generate the output data matrix and the values of the output data matrix relate linearly to the red blood cell concentration at each pixel.

Importantly, the ability of the computing device to use the three matrixes in an algorithm to form the output data matrix representing the red blood cell concentration of the microcirculation avoids or significantly reduces not only distortion problems from multiple scattering in tissue, but also the adverse effects from fluctuating light intensity from an illuminating device. The algorithm which is provided to generate the output data matrix from the red, blue and green data matrixes can take various forms. According to claim 17, the algorithm

employs the difference of the values of the data matrixes representing red and green colors divided by the sum of the corresponding values of the data matrixes representing red and green colors. According to claim 36, the algorithm employs the difference of the values of the data matrixes representing red and green colors divided by corresponding values of the data matrix representing blue color. According to claim 37, the algorithm employs the difference of the values of the data matrixes representing red and green colors divided by corresponding values of data matrixes representing the difference between red and blue colors. According to claim 38, the algorithm employs the difference of the values of the data matrixes representing red and blue colors divided by corresponding values of the data matrix representing green color. The claimed system, including the computing device using an algorithm based on a principle that eliminates the adverse effects of multiple scattering and alterations in the illumination, is neither taught nor suggested by the cited prior art.

In the Official Action, claims 12, 14, 15 and 20-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Groner et al U.S. Patent No. 5,983,120, alone or in view of the Shih U.S. Patent No. 6,061,176, the Godik U.S. Patent No. 5,699,797, the Nilsson U.S. Patent No. 5,361,769 and the Zinser et al U.S. Patent No. 5,620,000. The Examiner asserted that Groner discloses a method and apparatus to perform in vivo analysis of blood vessels to determine blood parameters such as concentrations and blood cell counts, and the apparatus includes a monochromatic and/or polarized illuminating light source, detecting means for detecting reflected light that is reflected from the illuminated object, a first polarizer to polarize light from the light source, and a second polarizer placed in a reflected light path between an illuminated object and the detecting means with a plane of polarization 90° relative to that of the first

polarizer. The Examiner asserted that Groner discloses that reflected light is captured by an image capturing means, which is coupled to a computer to carry out scene segmentation and correction for blood characteristic analysis (column 8, lines 55-68).

The Examiner alternatively relied on Shih as disclosing an analog-to-digital converter to convert detected light into digital values and directly displaying images of circulation on a monitor, on Zinser et al as teaching the use of a matrix MxN of measured values which are subject to Fourier transform, on Nilsson as delivering measurement values to a computer 7 to determine blood circulation, along with a color monitor to display microcirculation in specific colors, and on Godik as disclosing display microcirculation behaviors of physiological liquids marked with the help of pseudo-colors which could be red, green, and blue. The Examiner asserted it would have been obvious to combine Groner with Shih, Zinser, Godik and Nilsson to use red, green and blue and to display microcirculation to increase visualization and to use a computer that separates data into matrices that are red, green and blue.

These rejections are traversed and reconsideration is respectfully requested. The system of claim 12 is nonobvious over and patentably distinguishable from the device of Groner et al, alone or in combination with the additionally cited references. More particularly, the apparatus of Groner et al utilizes reflected (white) light, and employs polarization filters and a photodetector array. However, Groner et al provide no teaching or suggestion of a computing device as included in the system of claim 12, and, particularly, a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and adapted to employ an algorithm to the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation. Additionally,

Groner et al provide no teaching, suggestion or recognition that such a system as claimed can reduce distortion from multiple scattering and from varying light intensity.

To the contrary, the Groner et al apparatus requires use of a clear representation of the object (e.g. blood vessels or individual blood cells embedded in a semitransparent tissue matrix) in such a way that no internal multiple scattering of the light is allowed. See, for example, the Groner et al claim 1 which recites image capturing means for capturing a reflected image reflected from the illuminated blood at a depth less than a multiple scattering length. This prerequisite of the Groner et al apparatus is also stated at column 7, beginning at line 58: "The tissue covering the image portion must be traversed by light without multiple scattering to obtain a reflected image"; and at column 7, beginning at line 65: "Second, the light that is collected from the subject must reach an image capturing means without substantial scattering, i.e. the reflected image must be captured from a depth that is less than the multiple scattering length. Accordingly, the Groner et al apparatus is only capable of investigating vascular networks close to the skin surface in transparent tissues, for example, the mucosa or in the transparent skin of newborn infants, and is dependent of the indicated clear view of the object under investigation.

In contrast to the Groner et al apparatus, the system of the present invention does not require a clear view of an object in tissue. Rather, because the computing device is adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and is adapted to employ an algorithm to the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation, the combined amount of diffusely backscattered light is analyzed to extract information about the average local red blood cell concentration modulating the pixels of the red, green and blue planes. This system

is immune to the Groner et al disadvantages of multiple scattering of light blurring the individual objects before the diffusely backscattered light reaches the photo-detector array for further analysis. To the contrary, the system of the present invention is not restricted to analyzing blood at a depth less than a multiple scattering length but rather operates via analysis of tissue at a multitude of scattering lengths. Groner et al provide no teaching or suggestion of a system which overcomes such a problem and particularly provide no teaching, suggestion or recognition of a system including a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and adapted to employ an algorithm to the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation as claimed.

The deficiencies of Groner et al are not resolved by the secondary references. Specifically, Shih was relied on as disclosing an analog-to-digital converter to convert detected light into digital values. However, Shih does not disclose a computing device adapted to separate collected digital values into data matrixes representing red, blue and green colors and adapted to employ an algorithm to create an output data matrix. Accordingly, Shih does not resolve the deficiencies of Groner et al.

Godik was relied on as disclosing a display of microcirculation behaviors of physiological liquids which is marked with the help of pseudo-colors. However, Applicants find no teaching by Godik of a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and to then employ an algorithm to the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation, and, importantly, Applicants find no motivation in Godak

to modify any of the teachings of Groner et al to result in a system as recited in claim 12. Thus, the pseudo-color image of Godik does not provide any suggestion of a system for generating, inter alia, data matrixes representing red, blue and green colors, respectively, and an output data matrix by employing an algorithm to the data matrixes. As noted in the present specification, the output data matrix which is generated by the computing device in the system of claim 12 may subsequently be presented as a pseudo-color or shaded image on a computer display (see page 9). However, Godik provides no teaching or suggestion of a system for obtaining a data output matrix as recited in claim 12 which may then be translated for pseudo-color representation. Thus, Godik tails to resolve the deficiencies of Groner et al.

Nilsson was relied upon as disclosing an apparatus that delivers measurement values to a computer to determine blood circulation and includes a color monitor to display microcirculation in specific colors. However, Applicants find no teaching by Nilsson of a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and to then employ an algorithm to the data matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation, and, importantly, Applicants find no motivation in Nilsson to modify any of the teachings of Groner et al to result in a system as recited in claim 12. Thus, the display of Nilsson does not provide any suggestion of a system for generating, inter alia, data matrixes representing red, blue and green colors, respectively, and an output data matrix representing the red blood cell concentration of the microcirculation by employing an algorithm to the data matrixes. As noted in the present specification, the output data matrix which is generated by the computing device in the system of claim 12 may subsequently be presented on a computer display. However, Nilsson

provides no teaching or suggestion of a system for obtaining a data output matrix as recited in claim 12. Thus, Nilsson fails to resolve the deficiencies of Groner et al.

Zinser et al was relied upon as teaching a computer that collects a matrix MxN of measured values and a second matrix MxN of measured values which are subject to FFT Fourier transform and that matrices can be displayed on the screen of the computer as an image. However, the MxN matrices of Zinser et al are obtain by moving a laser beam along a line of a scanned object, and measuring the intensity of the light reflected during the scanning at fixed time intervals so that a series of M-measured values is obtained along the scanned line which represent the reflected light intensities at M-individual points along this scanned line. The scanning along this first line of the object is repeated successively N-times so that each of the M-points along the line is measured N times at equal time intervals of 1/f, thus forming a matrix of MxN measured values (column 5, lines 46-65). However, Zinser et al provide no teaching of a device or method which generates, inter alia, data matrixes representing red, blue and green colors, respectively, and an output data matrix by employing an algorithm to the red, blue and green data matrixes. Thus, Zinser et al's data matrices are not relevant to the computing device in the system of claim 12 and Zinser et al fail to resolve the deficiencies of Groner et al.

Crutchfield was relied on as disclosing administration of vasoactive drug. However, Crutchfield does not resolve the deficiencies of Groner et al and, specifically, does not teach a system comprising, inter alia a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and adapted to employ an algorithm to the separated matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation as required by claim 12. Further, Applicants find no

apparent reason of record for one of ordinary skill in the art to use any of the Crutchfield teachings to modify Groner et al.

Nakakuki was relied on as teaching that image data corresponding to red, green and blue may be divided into a group of pixels in a matrix and the luminance for each pixel may be represented as 8-bit data. However, Nakakuki is directed to an image processing program for performing image correction on image data captured under backlighting conditions, i.e., when a photograph is taken with a very bright background (paragraphs [0003] and [0005]). Nakakuki is not directed to systems or methods for determining microcirculation and provides no teaching or suggestion of a system for determining microcirculation based on a measured concentration of red blood cells. Additionally, Nakakuki disclose that for color image data, the image data corresponding to red, green and blue may be divided into a group of pixels in a matrix, the luminance for each pixel is converted into a numerical value on a scale, and the relationship between a luminance and the number of pixels having that luminance is reviewed to control, for example, exposure timing for the image (see, for example, paragraphs [0031] and [0044]).

Nakakuki does not teach or suggest a computing device adapted to separate collected information into data matrixes representing red, blue and green colors, respectively, and adapted to employ an algorithm to the separated matrixes to generate an output data matrix representing the red blood cell concentration of the microcirculation, and one of ordinary skill in the art would have had no apparent reason to combine the teachings of Nakakuki with Groner et al to provide such a device. Neither Nakakuki not Groner et al teach or suggest the use of a computing device that employs an algorithm that normalizes data matrixes representing red, blue and green colors into an output matrix representing a concentration of red blood cells with respect to variations in

total light intensity from the illumination device and multiple scattering. Accordingly, the combination of Nakakuki and Groner et al cannot render obvious a computing device employing an algorithm that provides an output matrix from data matrixes of red, blue and green colors that represents red blood cell concentration in tissue without distortion and dependence of the illuminating light level. Thus, Nakakuki fails to resolve the deficiencies of Groner et al.

Finally, Takahashi et al disclose an illumination device for observing and photographing a portion of a body cavity to be examined with an endoscope and including a bundle of optical fibers. However, the Takahashi et al teachings are not directed to systems or methods for determining microcirculation and they provide no teaching or suggestion of a system for determining microcirculation based on a measured concentration of red blood cells. Importantly, Applicants find no apparent reason of record for one of ordinary skill in the art to use any of the Takahashi et al teachings to modify the Groner et al, particularly along the lines of the present system.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine known elements in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). Applicants find no evidence of record which would indicate any apparent reason to one of ordinary skill in the art to modify and supplement the teachings of Groner et al to result in a system as presently claimed which is operable to generate an output data matrix from data matrixes of red, blue and green colors, representing the red blood cell concentration of the microcirculation and avoiding adverse effects of illumination and multiple scattering. Thus, the requisite showing that those of ordinary skill

in the art would have had some apparent reason to modify the Groner et al system in a way that would result in the claimed system has not been made.

Accordingly, the system for determining microcirculation according to claim 12, and claims 13-22 and 36-38 dependent thereon, is nonobvious over and patentably distinguishable from the cited combinations of references based on Groner et al, and the rejections under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Official Action and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the application is not in condition for allowance, the Examiner is encouraged to call the undersigned to resolve any outstanding matters. Please charge any fee required with this response to Deposit Account No. 503915.

Respectfully submitted,

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